Atty Dkt. No. 8500-0258
Serial No. 09/780,990
Reference No. BB

PATENT SPECIFICATION

(11) 1 277 265

NO DRAWINGS

(21) Application No. 38168/69 (22) Filed 30 July 1969
(31) Convention Application No. 748 606 (32) Filed 30 July 1968
(31) Convention Application No. 825 974 (32) Filed 19 May 1969 in
(33) United States of America (US)
(45) Complete Specification published 7 June 1972
(51) International Classification C07C 169/26; A61K 17/06
(52) Index at acceptance C2U 2 4A1 4A2 4C4 4C5 4D 4X

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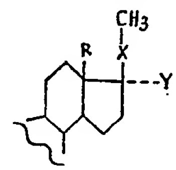
1 277 265

(54) 6-SUBSTITUTED-13-POLYCARBONALKYL-18,19-DINORPREGN-4-EN-3-ONES

(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York City 17, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

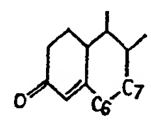
This invention is concerned generally with novel steroid compounds and with processes for preparing and using the same. More particularly it relates to steroids of the 6-substituted-13-polycarbonalkyl-18,19-dinorpregn-4-en-3-one series and the Δ^6-dehydro analogues thereof, and to processes for producing them.

The steroid compounds of this invention have in rings C and D the structure



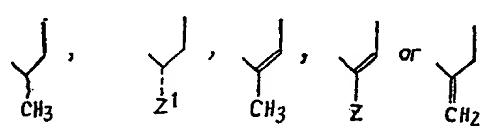
(I)

wherein R is an alkyl group of from 2 to 6 carbon atoms; X is C=O or C(H)OR^1 wherein R^1 is a hydrogen or a (lower)alkanoyl group; and Y is H, OH or OCOR^2 wherein R^2 is a (lower)alkyl group and in rings A and B the structure

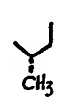


(P)

wherein C_6—C_7 is a divalent radical of one of the structures:



wherein Z is chloro, bromo or fluoro and Z^1 is chloro or bromo, provided that when X is C=O and Y is H, —C_6—C_7 is other than



(Q)

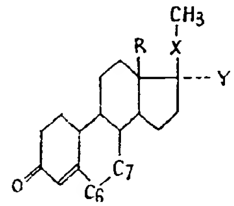
The term "(lower)alkyl" denotes ethyl groups of from 1 to 6 carbon atoms, including both straight and branched chain, and illustrative members of which are methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl and hexyl. The

[*Price 25p*]

term "polycarbon alkyl" denotes polycarbon(lower)alkyl, containing from 2 to 6 carbon atoms and includes groups illustrated above, but excluding the methyl group; the ethyl group is preferred. The term "(lower)alkanoyl" denotes groups of the formula (lower)-alkyl—CO—, wherein "(lower)alkyl" is above defined; acetyl is preferred.

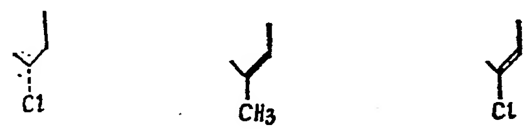
Special mention is made of a number of particularly valuable preferred compounds of the instant invention. There are:

compounds of formula Ia:



(Ia)

wherein R is alkyl of from 2 to 6 carbon atoms; X is C=0 or C(H)OR^1 wherein R^1 is hydrogen or (lower)alkanoyl; Y is H, OH or $OCOR^2$ wherein R^2 is (lower)alkyl; and $—C_6—C_7—$ is a divalent radical of one of the structures



13β-ethyl-20ξ-hydroxy-6-methyl-18,19-dinorpregna-4,6-dien-3-one, a compound of formula Ia wherein R is ethyl, X is C(H)OH), Y is H and $—C_6—C_7—$ is

13β-ethyl-17α-hydroxy-6-methyl-18,19-dinorpregna-4,6-diene-3,20-dione and the 17α-acetate ester thereof, i.e. compounds of formula Ia wherein R is ethyl, X is C=O, Y is OH or $OCOCH_3$, respectively, and $—C_6—C_7—$ is

13β-ethyl-6α-chloro-18,19-dinorpregn-4-en-3-on-20ξ-ol acetate, a compound of formula Ia wherein R is ethyl, X is C(H)$OCOCH_3$, Y is H and $—C_6—C_7—$ is

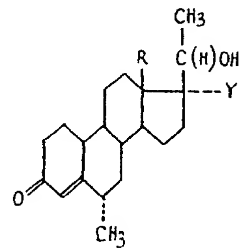
13β-ethyl-6-chloro-18,19-dinorpregna-4,6-dien-3-on-20-ol acetate, a compound of formula Ia wherein R is ethyl, X is C(H)$OCOCH_3$, Y is H and $—C_6—C_7—$ is

13β-ethyl-6α-chloro-18,19-dinorpregn-4-ene-3,20-dion-17α-ol acetate, a compound of formula Ia wherein R is ethyl, X is C=O, Y is $OCOCH_3$, and $—C_6—C_7—$ is

13β-ethyl-6-chloro-18,19-dinorpregna-4,6-diene-3,20-dion-17α-ol acetate, a compound of formula Ia wherein R is ethyl, X is C=O, Y is $OCOCH_3$ and $—C_6—C_7—$ is

13β-ethyl-6-chloro-17α-hydroxy-18,19-dinorpregna-4,6-diene-3,20-dione, a compound of formula Ia wherein R is ethyl, X is C=O, Y is OH and $—C_6—C_7—$ is

compounds of formula Ib:

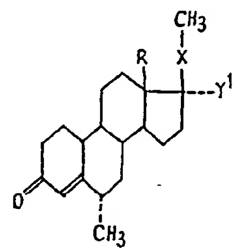


(Ib)

wherein R is alkyl of from 2 to 6 carbon atoms; and Y is H, OH or $OCOR^2$ wherein R^2 is (lower)alkyl.

13β-ethyl-20ξ-hydroxy-6α-methyl-18,19-dinorpregn-4-en-3-one, a compound of formula Ib wherein R is ethyl, X is C(H)OH and Y is H;

compounds of formula Ic:



(Ic)

wherein R is alkyl of from 2 to 6 carbon atoms; X is C=O or C(H)OH; and Y^1 is OH or $OCOR^2$ wherein R^2 is (lower)alkyl; and

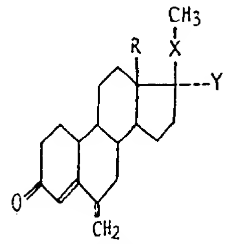
13β-ethyl-17α-hydroxy-6α-methyl-18,19-dinorpregn-4-ene-3,20-dione acetate, a compound of formula Ic wherein R is ethyl, X is C=O and Y^1 is $OCOCH_3$.

The compounds of formula I except the 6-methylene compounds are valuable hormonally-active substances. They have been found to be active in standard pharmacological tests in laboratory animals such as mice, rats and rabbits, progrestationally and anti-estrogenically. They are more active than many known compounds now used with these activities and, in addition, possess a valuable separation of hormonal properties to a greater degree than many compounds presently used with these activities. Progestationally-active substances are used in cases of infertility and more specifically, but without limitation, to delay estrus and ovulation in cattle, pigs, and dogs. Anti-estrogenically active compounds are administered to counter the effects due to an excess of estrogen, such as estrone and similar metrotropic agents. The instant compounds are also of value in that field of use known as microdose contraception. They have an anti-fertility effect at considerably lower levels of adiminstration than the levels used conventionally, e.g. 1 mg. to 100 mg., on a daily basis. The 6-methylene compounds of formula I are intermediates.

The compounds of formula I of this invention can be prepared by a method comprising:

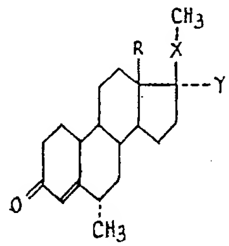
(a) hydrogenating, for example by exchange hydrogenation with a suitable organic

hydrogen-donor, e.g. cyclohexane, in the presence of a catalyst, e.g. palladium on carbon, a 6-methylene compound of formula II:



(II)

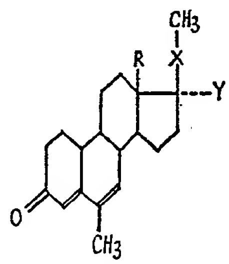
wherein R, X and Y are as hereinabove defined to give a compound of formula Id:



(Id)

wherein R, X and Y are as herein above defined;

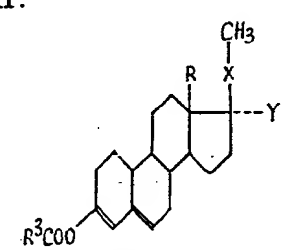
(b) rearranging, for example by heating with a weak base, e.g. sodium acetate, and a noble metal catalyst, preferably a Pt or Pd catalyst, e.g. Pt or Pd/C, in an inert solvent, e.g. ethanol, a 6-methylene compound of formula II hereinabove to give the corresponding compound of formula Ie:



(Ie)

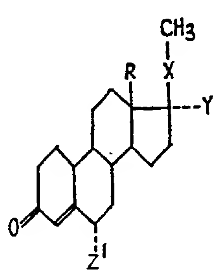
wherein R, X and Y are as hereinabove defined;

(c) chlorinating or brominating. e.g. with N-chlorosuccinimide or N-bromosuccinimide, an enol ester of formula III:



(III)

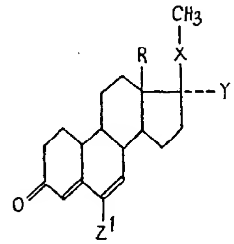
wherein R, X and Y are as above defined and R^3 is (lower)alkyl, to give a compound of formula If:



(If)

wherein R, X, Y and Z^1 are as above defined;

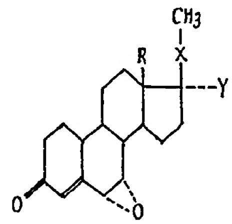
(d) directly dehydrogenating, e.g. by heating with chloranil, a compound of formula If to give a compound of formula Ig:



(Ig)

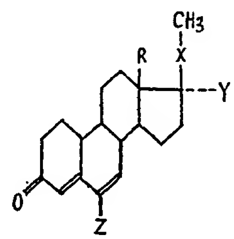
wherein R, X, Y and Z^1 are as above defined; or preferably

(e) reacting with a hydrogen halide, namely dry hydrogen chloride, hydrogen bromide or hydrogen fluoride an epoxide of formula IV:



(IV)

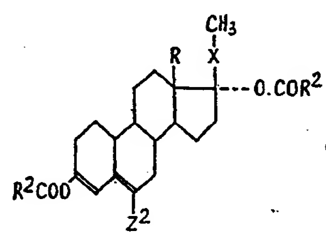
wherein R, X and Y are as hereinabove defined, to give a compound of formula Ih:



(Ih)

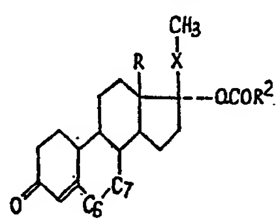
wherein R, X, Y and Z are as above defined;

(f) partially hydrolysing a compound of formula Ik:



(Ik)

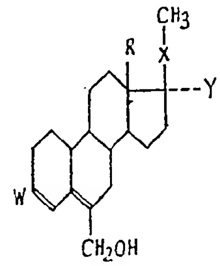
wherein Z^2 is methyl, bromo or chloro, to give a compound of formula Ij:



(Ij)

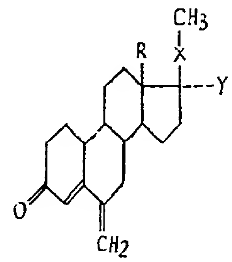
wherein R, R^2 and $—C_6—C_7—$ are as defined in formula I hereinabove and ring B is saturated, with a 6-methyl, chloro or bromo substituent;

(g) hydrolysing a compound of the formula In



(In)

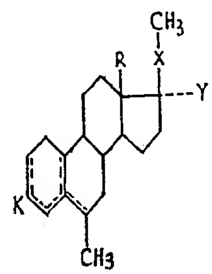
preferably with dilute mineral acid or an organic acid to give a compound of the formula



(II)

wherein the groups R, X and Y are as defined above and W is an alkoxy group;

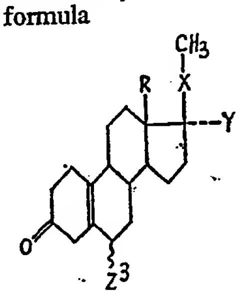
(h) hydrolysing a compound of the formula



(a)

where K is a protected oxo group which in conjunction with unsaturation in rings A and/or B indicated by dotted lines is hydrolysable by acid or a 4,5-ethylenic 3-ketone, and X is as defined above or may be a protected carbonyl or hydroxy-methylene group to obtain a compound of formula Id and/or the corresponding 6β-methyl compound, or

(i) isomerising a compound of formula



(Io)

wherein Z^3 is methyl, α-chloro or α-bromo to obtain a corresponding gon-4-en-3-one.

The starting materials of formula In and intermediates therefor are described and claimed in our copending application 32415/71 (Serial No. 1277268) which is divided from the present application.

The method of step (a), i.e. hydrogenating a 6-methylene compound of formula II can be carried out by an exchange hydrogenation technique. In this method, for example, a mixture of the 6-methylene compound with about 3 parts by weight of cyclohexene and about 1/5 parts by weight of a catalyst, such as 5% palladium on carbon, is refluxed in absolute ethanol for about ½ to about 4 hours. The product of formula Id is recovered by any standard technique. One useful method comprises adding ether,

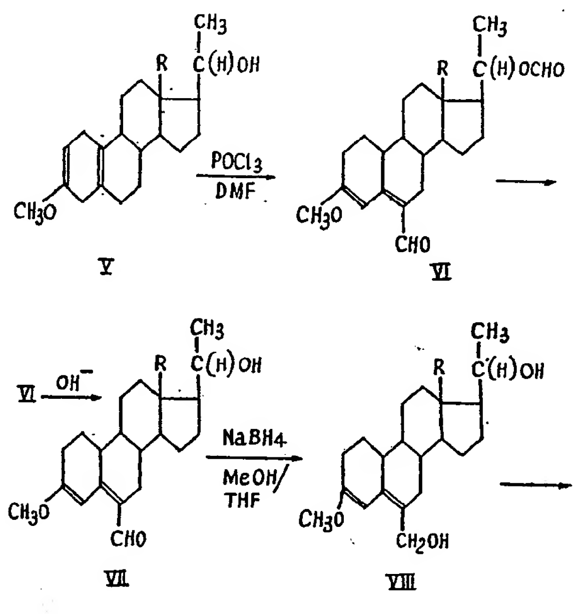
filtering the mixture, adding a trace of mineral acid and evaporating off the solvent to leave the product as a residue. It may, if desired, be purified by recrystallisation from ether.

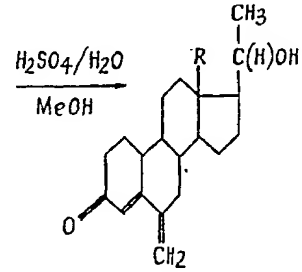
The method of step (b), i.e. rearranging a 6-methylene compound of formula II can be carried out by treating it with a weak base in the presence of a catalyst, such as palladium on carbon and in an inert solvent, preferably at moderately elevated temperatures, e.g. 75 to 100°C. In one manner of proceeding, the compound of formula II is suspended in about 300 parts by weight of an alcohol, e.g. ethanol, and there is added about 0.5 parts by weight of sodium acetate and about 0.15 parts of 5% palladium on carbon. If the mixture is heated and refluxed for about 1 to 3 hours, rearrangement to the compound of formula Ic is substantially complete. This can be recovered in any conventional way but a convenient means is to cool the mixture, dilute it with ether, filter it, wash with saturated aqueous sodium bicarbonate, then with brine, dry over anhydrous sodium sulphate, and finally evaporate the solvents leaving the product as a residue. It may, if desired, be purified by recrystallisation from ether.

A useful series of compounds outside the scope of this invention, namely, the 13-polycarbonalkyl-6α-methyl-18,19-dinorpregn-4-ene-3,20-diones, can be prepared by treating the corresponding compounds of formula Id wherein R is polycarbonalkyl, X is CH(OH) and Y is H with a standard oxidising agent, e.g. the Jones reagent, 8*N* chromic acid, until conversion to a corresponding compound wherein X is C=O is substantially complete, and recovering said compound, which has valuable progestational and anti-estrogenic properties.

Starting materials of formula II hereinabove may be obtained for example according to one of the pathways outlined as follows.

In the first, a 13-alkyl-20-hydroxy-3-alkoxy-18,19-dinorpregna-2,5(10)-diene (V) is subjected to a Vilsmeier reaction ($POCl_3$ in dimethylforamide) to obtain the corresponding 13-alkyl-6-formyl-20-hydroxy-3-alkoxy-18,19-dinorpregna-3,5(6)diene 20-formate (VI). Compound VI is hydrolysed, as with potassium hydroxide in methanol, to the corresponding alcohol (VII) which, on treatment with a metal hydride reducing agent, e.g. sodium borohydride in methanol mixed with tetrahydrofuran, affords the 13-alkyl-20-hydroxy-6-hydroxymethyl-3-alkoxy-18,19-dinorpregna-3,5(6)-diene (VIII). Treatment of compound VIII with acid, e.g. a mineral acid such as dilute methanolic H_2SO_4, conveniently at about 25°C results in hydrolysis of the enol ether and concomitant elimination of water to give the 13-alkyl-20-hydroxy-6-methylene-18,19-dinorpregn-4-en-3-one of formula IIa (R is as hereinabove defined and X is C(H)OH):



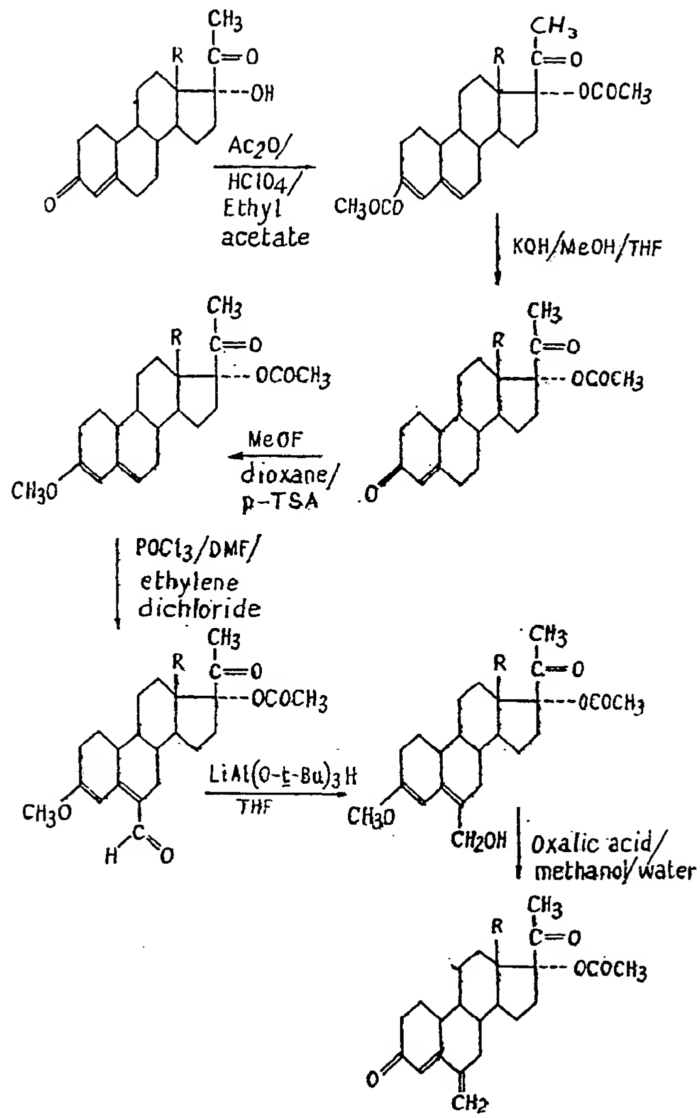
VIII 

IIa

wherein "DMF" is dimethylformamide and "THF" is tetrahydrofuran. In the above scheme the 3-alkoxy group is conveniently a methoxy group but other alkoxy groups may of course be used and this route provides access to the 3-alkoxy compounds Im and In (corresponding to compound VIII of the above scheme).

In the second, the starting material, a 13β-alkyl-17α-hydroxy-18,19-dinorpregn-4-ene-3,20-dione is treated with an acylating agent, e.g. acetic anhydride and a trace of perchloric acid in ethyl acetate, to obtain the corresponding 13β-alkyl-3,17-dihydroxy-18,19-dinorpregna-3,5-dien-20-one diacylate e.g. diacetate, which is then reacted with a base, e.g. methanolic potassium hydroxide in tetrahydrofuran, to obtain the corresponding 13β-alkyl-17-hydroxy-18,19-dinorpregn-4-ene-3,20-dione acylate e.g. acetate, which in turn is reacted with methyl orthoformate in dioxane containing *p*-toluenesulphonic acid to produce the corresponding 13β-alkyl-17-hydroxy-3-methoxy-18,19-dinorpregna-3,5-dien-20-one acylate e.g. acetate, which in turn is formylated with phosphorus oxychloride in dimethylformamide and ethylene dichloride to produce the corresponding 13β-alkyl-6-formyl-17α-hydroxy-3-methoxy-18,19-dinorpregna-3,5-dien-20-one acylate e.g. acetate, which is reduced with lithium aluminium tri-*t*-butoxy-hydride in tetrahydrofuran to the corresponding 13β-alkyl-17α-hydroxy-6-hydroxymethyl-3-methoxy-18,19-dinorpregna-3,5-dien-20-one acylate e.g. acetate; and treatment of this with oxalic acid in methanol and water produces the

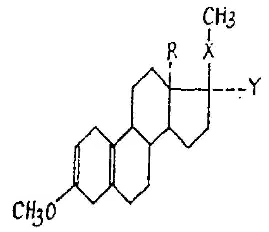
desired 13β-alkyl-17α-hydroxy-6-methylene-3-methoxy-18,19-dinorpregn-4-ene-3,20-dione acylate e.g., acetate according to the following sequence:



wherein R is as hereinabove defined, "THF" is tetrahydrofuran, "p-TSA" is *p*-toluenesulphonic acid and "MeOF" is methyl orthoformate. Of course other alkylating agents may be used in place of "MeoF".

The method of step (c), i.e. chlorinating an enol ester of formula III with a reagent such as N-chlorosuccinimide or N-bromosuccinimide, can be carried out by adding the enol ester to about 30 parts of a (4:1) mixture of acetone, and water, which contains about 0.7 parts of sodium acetate and 0.7 parts of glacial acetic acid per part by weight of enol ester. The mixture then is cooled to about 5°C and there is added about 6 to 8 parts of N-chlorosuccinimide per part by weight of enol ester. The formation of the product of formula If is complete in about 1 to about 4 hours and it can be recovered by diluting the reaction mixture with water, then extracting with ether and evaporating to dryness leaving compound If as a residue. If, instead of N-chlorosuccinimide, N-bromosuccinimide is used, there is obtained the corresponding 6-bromo compound of formula If.

Starting materials of formula III hereinabove may be prepared from an enol ether of formula Vb:



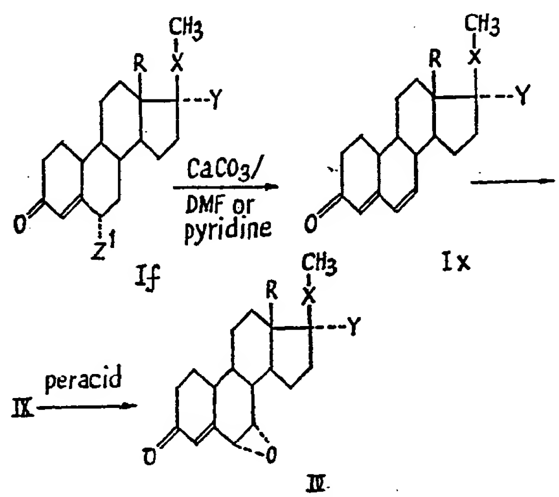
(Vb)

(wherein R, X and Y are as above defined), by acid hydrolysis, e.g. with methanol: concentrated HCl: water 90:6:4, or of the cyclic 20-ethylene ketal corresponding to the compound of formula Vb where X is C=O; by acylating with an acid anhydride, preferably acetic anhydride in the presence of a trace of perchloric acid and a substantial amount of ethyl acetate. The acylating reaction is quite rapid, being substantially complete in about 15—20 minutes. Treatment with enough aqueous sodium bicarbonate to destroy excess acetic anhydride and evaporation of the organic layer to dryness, provides Compound III as a residue.

The method of step (d), i.e. dehydrogenation of a compound of formula If to introduce a double bond between C_6 and C_7 can be carried out with a reagent such as chloranil. In one manner of proceeding, compound If can be suspended in 25 parts by weight of a solvent, such as ethyl acetate, containing about 5 parts by weight of acetic acid and about 2 parts by weight of chloranil per part by weight of If is added. If the mixture is refluxed under nitrogen for about 24 hours, conversion to compound Ig is substantially complete and it may be recovered, for example, by cooling the mixture, washing it with 10% sodium hydroxide solution, then with brine, drying it over anhydrous sodium sulphate and, finally, evaporating to dryness, leaving Ig as a residue.

The method of step (e), i.e. treatment of the epoxide of formula IV with a halogen acid to provide the 6-halo-4,6-diene of formula Ih can be carried out with dry hydrohalic acids. In one manner of proceeding, the epoxide (IV) can be suspended in about 50 parts by weight of glacial acetic acid. The mixture is cooled to about the freezing point of glacial acetic acid, 16.6°C, and a slow stream of gaseous hydrogen chloride, hydrogen bromide or hydrogen fluoride is passed through. After about 2 to 6 hours, the formation of the compound of formula Ih is substantially complete and the product can, for example, be recovered by pouring the mixture into ice water and extracting with a water-immiscible solvent, such as a mixture of 10:1 benzene and ether. The organic layer is washed free of acid, e.g. with dilute sodium bicarbonate, dried and evaporated to leave compound Ih as a residue.

Starting materials of formula IV hereinabove, the epoxides, may be prepared by halogen elimination in the 6-chloro or -bromo compound of formula If, to provide the 4,6-diene (IX) followed by epoxidation thereof to provide compound IV according to the following:

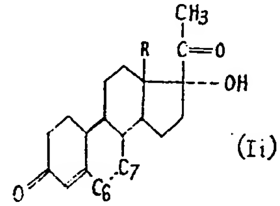


wherein R, X, Y and Z^1 are as hereinabove defined and "DMF" is dimethylformamide.

The dehalogenation is accomplished, for example, by suspending compound If in about 50 parts by weight of dimethylformamide or pyridine and adding about 3 parts by weight of calcium carbonate based on parts by weight of If. Refluxing under nitrogen for about 1 hour, filtering off the solid, pouring the filtrate into water, extracting with ether and evaporation of the ether leaves the 4,6-diene IX as a residue. This is epoxidised, for example, by suspending it in about 50 parts by weight of chloroform and treating the mixture with 1 part by weight of a peracid, such as perbenzoic and/or preferably monoperphthalic acid, per part by weight of IX, for about 48 hours at about 22°C. The epoxide IV is then recovered, for example, by washing the organic phase with saturated sodium bicarbonate, then with brine, drying it over sodium sulphate and evaporating the solvent to leave IV as a residue.

The partial hydrolysis step (f) may be carried out with dilute alkali metal hydroxide, such as potassium hydroxide in methanol e.g. 2% methanolic potassium hydroxide.

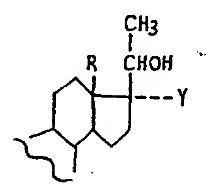
The compound of formula Ik may be obtained by acylation of a compound of formula Ii (wherein R, is defined above) and C_6—C_7 is as defined in connection with formula I but having a saturated ring B nad excluding 6-methylene compounds with a reagent of the formulae $(R^2CO)_2O$ or R^2COCl or, preferably, a mixture thereof in the presence of an acid binding agent, e.g. an organic base such as dimethylaniline, N-methyl-morpholine or, preferably, pyridine, after processes being carried out if required to obtain the desired substituent at the 20-position.



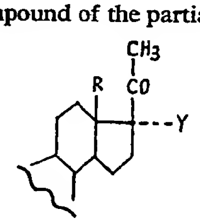
(Ii)

The method of step (f), i.e. selectively hydrolysing a compound of formula Ik including preparation of the diacylate intermediate, is preferably carried out stepwise, first with an appropriate acyl anhydride, e.g. acetic anhydride, or an acyl halide, e.g. acetyl chloride or acetyl bromide, or preferably mixtures thereof, in the presence of an acid binding agent, such as an organic base, preferably pyridine, to form the corresponding enol ester 17α-acylate. In one manner of proceeding, compound Ii is treated with an excess of acetic anhydride and acetyl chloride in pyridine and the mixture is warmed to about 50—75°C for a few minutes then kept at about 23°C for about 67 hours. The enol ester is recovered by pouring the mixture into a large volume of water and extracting the organic layer with ether; washing, drying and evaporating the ether leaves the enol ester as a residue. This is selectively hydrolysed with a dilute base. In one manner of proceeding, the enol acetate is suspended in 2% methanolic potassium hydroxide and the mixture is stirred at 0°C until partial hydrolysis is substantially complete. Cooling and neutralising the reaction mixture, evaporating to dryness, extracting the residue with ether and evaporating the ether, leaves compound Ij as a residue.

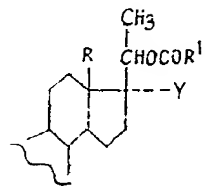
Compounds of formula I may be interconverted to other compounds of formula I by effecting changes in the substituent at the 20-position. Thus a compound of the partial formula



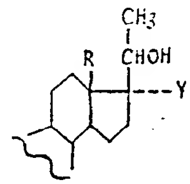
may be selectively oxidised to a compound of the partial formula



wherein R and Y are as defined above; and a compound of the partial formula



may be selectively hydrolysed to give a compound of the partial formula



wherein R, R¹ and Y are as defined above;

The selective oxidation can be carried out with Jones reagent where Y is hydrogen or OCOR² and with dimethylsulphoxide in acetic acid where Y is OH.

The compounds described herein may also be made by processes known for analogous compounds.

Starting material for all of the above-mentioned compounds can be made by various processes including hydrogenation of a corresponding 16-ene to give a corresponding compound in which Y is hydrogen (as described in British Application No. 3266/71 (Serial No. 1277267)) or by processes described for analogues in British Specification 1,199,605. Other starting materials are shown in or can be derived from those described in U.K. Patent 1,115,635, May 29, 1968. Starting materials in which R is other than ethyl can be derived from compounds analogous to those described in U.K. Specification 1,115,635. They may be made by applying, in earlier steps, methods of total synthesis described by Douglas, Graves, Hartley, Hughes, McLoughlin, Siddall and Smith in J.Chem.Soc. *1963*, 5072—5094; and by H. Smith, Hughes, Douglas, Wendt, Buzby, Jr., Edgren, Fisher, Foell, Gadsby, Hartley, Herbst, Jansen, Ledig, McLoughlin, McMenanim, Pattison, Phillips, Rees, Siddall, Suida, L. Smith, Tokolics and Watson in J.Chem.Soc., *1964*, 4472—4492. If starting materials are the product of a total synthesis which has not included a suitable resolution stage the compounds of the invention will be present as racemates. However, if a resolved starting material is used (obtained for example by resolving at an earlier stage in the synthesis) the products of the processes described here will of course be the resolved *d*-enantiomers. Suitable resolved intermediates for starting materials of the invention are described in the literature, e.g. J. Med.Chem. *1967*, 199—204. Using a convention approved by Fieser and Fieser, "Steroids", p.336 (1959), the compound designated as the *d*-forms are the enantiomers corresponding in configuration at C—13 to that of the natural hormone estrone. The corresponding enantiomorphs are consequently designated the *l*-forms and the racemates the *dl*-forms. The structural formulas show only the enantiomorphs of the d-configuration but it will of course be understood that the racemates are included in the invention.

The time and temperature ranges used in carrying out the above mentioned processes are not particularly critical and, as will be readily apparent to those skilled in the art, will be selected to carry out the reaction in minimum of time without undue difficulty. Thus, reaction temperatures below those exemplified can be used, but then the reaction time is extended. On the other hand, reaction temperatures higher than those exemplified can be used with a concomitant decrease in reaction time, although purity of the product may be somewhat decreased.

As is mentioned hereinabove, the compounds of formula I except the 6-methylene compounds have progestational and anti-estrogenic activity, and they are also useful to prepare compounds with these activities. The progestational activity is illustrated by standard pharmacological tests in warm-blooded lower animals. In one such test, the Clauberg assay, immature female rabbits are primed with estradiol-17β for six days. The primed rabbits then receive graded doses of the compound daily for five days before autopsy on the sixth. Progestational activity is assessed by histological evaluation of uterine glandular proliferation according to Elton and Edgren, Endocrinology, *63*, 464—472 (1958). The anti-estrogenic activity also is illustrated by standard pharmacological tests in warm-blooded lower animals. In one such test, the estrogen

antagonist-mouse uterine growth assay, 100 μg., of estriol is administered simultaneously with graded doses of the test compound over three days. At autopsy on day four, the uteri are removed and weighed. Active materials inhibit the metrotropic effect of estriol, as illustrated by Edgren and Calhoun, Experientia, *16*, 188 (1960).

The products of formula I of this invention except the 6-methylene compounds can be used for the above pharmacological purposes in association with a non-toxic carrier. They can be formulated in liquid or solid forms, for instance as capsules, tablets, suppositories, powders, dispersible granules or catchets, by combining them with conventional carriers. Such conventional carriers include magnesium carbonate or stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting wax and cocoa butter. Diluents, flavouring agents, solubilisers, lubricants, suspending agents, binders or tablet-disintegrating agents can be used. Powders or tablets preferably contain 5 or 10 to 99% of the active constituent. The active steroid can be formulated with an encapsulating material with or without other carriers.

Liquid preparations such as solutions, suspensions or emulsions can also be used. Such preparations include dispersions in a non-toxic carrier such as arachis oil or sterile water, preferably containing a nonionic surface active agent such as fatty acid esters of polyhydroxy compounds, e.g. sorbitan, aqueous starch in sodium carboxymethyl cellulose solutions, aqueous propylene glycol or polyethylene glycol. Thus a water-propylene glycol solution can be used for parenteral injection and aqueous suspensions suitable for oral use can be made by utilising natural or syntehtic gums, resins, methyl cellulose or other well known suspending agents.

The composition can be administered to the warm-blooded lower animals in unit dose form in which the dose unit is for instance from about 0.1 to about 200 mg. of each active steroid. The unit dose form can be a packaged composition, e.g. packeted powder, vials, or ampules or, for example, in the form of capsules, cachets or tablets or any number of these in packaged form. The compositions can also consist substantially solely of the active steroid when this is in unit dose form. When used for the purposes stated above, the dosage of the compounds will vary with the conditions being treated, but in general will be in the range established for progesterone (Merck Index. Seventh Edition, p.856 (1960)).

Description of the Preferred Embodiments:—The following examples are given by way of illustration and are not to be construed as limitations of this invention, variations of which are possible without departing from the scope thereof.

Example 1

13β-Ethyl-20ξ-hydroxy-6α-methyl-18,19-dinorpregn-4-en-3-one

(a) *dl*-13β-Ethyl-6-formyl-3-methoxy-18,19-dinorpregna-3,5-dien-20-ol formate:—To a solution of distilled dimethylformamide (0.65 g.) in distilled ethylene dichloride 1.0 ml.) at 0°C is added a solution of distilled phosphorus oxychloride (0.69 g.) in ethylene dichloride (3.0 ml.) over 30 minutes. After stirring an additional 10 minutes at 0°C, pyridine (1 drop) is added and then a solution of *dl*-13β-ethyl-3-methoxy-18,19-dinorpregna-2,5(10)-dien-20ξ-ol (0.66 g.) in ethylene dichloride (10 ml.) containing pyridine (100 mg.) is added all at once. After stirring the red solution at 0°C for 1 hours a solution of sodium acetate (4.0 g.) in water (40 ml.) is added and the mixture is stirred vigorously for 10 minutes. The mixture is poured into water, extracted with ether, the organic layer washed with water until the washings are colourless, dried over anhydrous sodium sulphate and stripped *in vacuo*. Trituration of the residue with methanol affords 0.34 g. of yellow-coloured product; m.p. 175—182°C, (softening from 170°C); λ_{max}^{KBr} 5.84, 6.07, 6.24 μ; λ_{max}^{EtOH} 220 mμ (ϵ 7,700), 321 mμ (ϵ 14,800).

(b) *dl*-13β-Ethyl-6-formyl-3-methoxy-18,19-dinorpregna-3,5-dien-20ξ-ol:—To a solution of *dl*-13β-ethyl-6-formyl-3-methoxy-18,19-dinorpregna-3,5-dien-20-ξol formate (2.65 g.) in tetrahydrofuran (100 ml.) under nitrogen at about 23°C is added all at once a solution of potassium hydroxide (1.35 g.) in methanol (100 ml.). Stirring at room temperature is continued for 30 minutes, the mixture is poured into saturated aqueous sodium bicarbonate and extracted with benzene. The benzene extracts are washed with water, dried over anhydrous sodium sulphate and stripped *in vacuo*. Trituration of the residue with ether affords 1.41 g. of yellow coloured product; m.p. 185—191°C. λ_{max}^{KBr} 3.03, 6.07, 6.24 μ; λ_{max}^{EtOH} 220 mμ (ϵ 9,400), 322 mμ (ϵ 15,400).

(c) *dl*-13β-Ethyl-6-hydroxymethyl-3-methoxy-18,19-dinorpregna-3,5-dien-20ξ-ol: To a solution of *dl*-13β-ethyl-6-formyl-3-methoxy-18,19-dinorpregna-3,5-dien-20ξ-ol (1.0 g.) in methanol (20 ml.) and tetrahydrofuran (20 ml. at room temperature is added sodium borohydride (250 mg.) all at once. The mixture is stirred at about 23°C for 15 minutes, poured into water and extracted with benzene. The organic layer is washed with water, brine, dried over anhydrous sodium sulphate and stripped *in vacuo*. Trituration of the residue with ether affords 0.45 g. of colourless product; m.p. 128—133°C; λ^{KBr}_{max} 3.04, 6.11, 6.21 μ; λ^{EtOH}_{max} 250 mμ (ε 17,800).

(d) *dl*-13β-Ethyl-20ξ-hydroxy-6-methylene-18,19-dinorpregn-4-en-3-one:—To a stirred slurry of *dl*-13β-ethyl-6-hydroxymethyl-3-methoxy-18,19-dinorpregna-3,5-dien-20ξ-ol (100 mg.) in methanol (1.0 ml.) at room temperature is added a trace of 8N sulphuric acid. Solution occurs immediately on adding the acid, and reprecipitation occurs after 2 minutes. After 5 minutes the precipitate is filtered giving 40 mg. of colourless product; m.p. 160—165°C and 215—222°C; λ^{KBr}_{max} 2.96, 6.04, 6.18, 6.30 μ; λ^{EtOH}_{max} 265 mμ (ε 11,300).

(e) *dl*-13β-Ethyl-20ξ-hydroxy-6α-methyl-18,19-dinorpregn-4-en-3-one:—A mixture of *dl*-13β-ethyl-20ξ-hydroxy-6-methylene-18,19-dinorpregn-4-en-3-one (650 mg.), cyclohexene (1.95 ml.) and Pd/C (5%, 130 mg.) in absolute ethanol (32.5 ml.) is heated at reflux for 45 minutes. The mixture is diluted with ether and filtered through filter-aid. A trace of concentrated hydrochloric acid is added and the solution is stripped *in vacuo*. Recrystallisation of the solid residue from ether affords 0.605 g. of colourless product; m.p. 162—168°C; λ^{KBr}_{max} 2.94, 6.05, 6.23 μ; λ^{EtOH}_{max} 241 mμ (ε 14,800); NMR has 4H at 5.85 ppm. 17H at 3.78 ppm (triplet), 6α CH_3 at 1.18 ppm (doublet, J 2 cps) and 21 CH_3 at 1.07 ppm (doublet, J c cps).

Analysis: Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37.
Found: C, 79.58; H, 10.24.

Example 2

13β-Ethyl-6α-methyl-18,19-dinorpregn-4-ene-3,20-dione

To a solution of *dl*-13β-ethyl-20ξ-hydroxy-6α-methyl-18,19-dinorpregn-4-en-3-one (600 mg.) in acetone (30 ml.) at 0°C. is added dropwise over 5 minutes Jones reagent (8N chromic acid, 0.05 ml.). Stirring at 0°C is continued for 10 more minutes and excess isopropanol is added. The mixture is diluted with ether, filtered through filter-aid, washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulphate and stripped *in vacuo*. The solid residue is recrystallised from ether giving 0.37 g. of off-white coloured product, m.p. 143—146°C; λ^{KBr}_{max} 5.90, 6.00, 6.24 μ; λ^{EtOH}_{max} 241 mμ (ε 15,900); NMR has 4 H at 1.09 ppm (doublet, J 6 cps).

Analysis: Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.53.
Found: C, 80.61; H, 9.33.

Example 3

13β-Ethyl-20ξ-hydroxy-6-methyl-18,19-dinorpregna-4,6-dien-3-one

A mixture of *dl*-13β-ethyl-20ξ-hydroxy-6-methylene-18,19-dinorpregn-4-en-3-one (100 mg.), sodium acetate (50 mg.) and Pd/C (5%, 15 mg.) in absolute ethanol (30 ml.) is heated at reflux for 1½ hours. The mixture is cooled to about 23°C, diluted with ether, filtered through filter-aid, washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulphate and stripped *in vacuo*. The solid residue is recrystallised from ether giving 22 mg. of colourless product; m.p. 204—205°C; λ^{KBr}_{max} 2.91, 6.05, 6.18, 6.31 μ; λ^{EtOH}_{max} 290 mμ (ε 22,800); NMR has vinyl protons at 5.93 ppm and 6.03 ppm, 17H at 3.75 ppm, 6 CH_3 at 1.80 ppm and 21 CH_3 at 1.12 ppm (doublet, J 5.5 cps).

Example 4

13β-Ethyl-17α-hydroxy-6α-methyl-18,19-dinorpregn-4-ene-3,20-dione acetate

(a) *dl*-13β-Ethyl-3,17-dihydroxy-18,19-dinorpregna-3,5-dien-20-one diacetate:— A solution of *dl*-13β-ethyl-17-hydroxy-18,19-dinorpregn-4-ene-3,20-dione (1.10 g.) in ethyl acetate (10 ml.) containing acetic anhydride (11.2 ml.) and perchloric acid (0.011

ml.) is stirred at room temperature for 5 minutes. The resulting yellow solution is diluted with ether, washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulphate and stripped *in vacuo*. Crystallisation of the gummy residue from methanol gives 1.03 g. of colourless product; m.p. 182—191°C; λ^{KBr}_{max} 5.71, 5.80, 5.89, 6.01 and no hydroxyl absorption; λ^{EtOH}_{max} 234 mμ (ϵ 17,600); NMR has vinyl protons at 5.47 ppm and 5.76 ppm, two acetate methyls at 2.11 ppm and C_{21} methyl at 2.09 ppm.

(b) *dl*-13,β-Ethyl-17α-hydroxy-18,19-dinorpregn-4-ene-3,20-dione acetate:—To a solution of *dl*-13,β-ethyl-3,17-dihydroxy-18,19-dinorpregna-3,5-dien-20-one diacetate (5.40 g.) in tetrahydrofuran (108 ml.) and methanol (108 ml.) is added under nitrogen at 0°C a 2% solution of potassium hydroxide in methanol (108 ml.). Stirring at 0°C is continued for 25 minutes. The mixture is poured into saturated aqueous sodium bicarbonate extracted with ether, and the organic layer washed with water, brine, dried over anhydrous sodium sulphate and stripped *in vacuo*, giving a colourless solid. Recrystallisation from ethyl acetate/hexane gives 4.22 g. of colourless product, m.p. 192—194°C; λ^{KBr}_{max} 5.80, 5.84, 6.01, 6.22.

(c) *dl* - 13β - Ethyl - 17α - hydroxy - 3 - methoxy - 18,19 - dinorpregna - 3,5 - dien - 20 - one acetate:—To a suspension of *dl* - 13,β - ethyl - 17 - hydroxy - 18,19 - dinorpregn - 4 - ene - 3,20 - dione acetate (3.0 g.) in dioxane (15.9 ml.) at room temperature is added methyl orthoformate (4.0 ml.) and a solution containing *p*-toluenesulphonic acid (0.16 g.) and methanol (0.36 ml.) in dioxane (1.75 ml.). The steroid dissolves after stirring 5 minutes and stirring is continued for another 55 minutes. Pyridine (8.5 ml.) is added and the mixture diluted with ether. Washing with water, brine, drying over anhydrous sodium sulphate and stripping *in vacuo* gives a gum. Crystallisation from methanol containing a trace of pyridine gives 1.81 g. of colourless product; m.p. 153—166°C; λ^{KBr}_{max} 5.79, 5.83 (shoulder), 6.06, 6.15.

(d) *dl* - 13,β - Ethyl - 6 - formyl - 17α - hydroxy - 3 - methoxy - 18,19 - dinorpregna - 3,5 - dien - 20 - one acetate:—To a solution of distilled dimethyl-formamide (7.25 ml.) and distilled ethylene dichloride (3.0 ml.) at 0°C is added a solution of distilled phosphorus oxychloride (1.50 g.) in ethylene dichloride (9.0 ml.) over 30 minutes. After stirring an additional 10 minutes at 0°C, pyridine (1 drop) is added and a solution of *dl* - 13,β - ethyl - 17α - hydroxy - 3 - methoxy - 18,19 - dinorpregna - 3,5 - dien - 20 - one acetate (1.70 g.) in ethylene dichloride (27 ml.) containing pyridine (15 drops) is added all at once. After stirring the red solution at 0°C for 1 hour a solution of sodium acetate (12.0 g.) in water (125 ml.) is added and the mixture stirred vigorously for 10 minutes. The mixture is extracted with ethyl acetate. The organic layer is washed with saturated aqueous sodium bicarbonate, water until the washings are colourless, dried over anhydrous sodium sulphate and stripped *in vacuo*. Trituration of the resulting gum with ether/hexane gives 1.29 g. of yellow coloured product; m.p. 182—187°C; λ^{KBr}_{max} 5.78, 5.83, 6.02, 6.19 (very strong), 6.28 (shoulder), 6.40 (shoulder); λ^{EtOH}_{max} 220 mμ (ϵ 9,400), 322 mμ (ϵ 15,800).

(e) *dl* - 13,β - Ethyl - 17α - hydroxy - 6 - hydroxymethyl - 3 - methoxy - 18,19 - dinorpregna - 3,5 - dien - 20 - one acetate:—To a solution of *dl* - 13,β - ethyl - 6 - formyl - 17 - hydroxy - 3 - methoxy - 18,19 - dinorpregna - 3,5 - dien - 20 - one acetate (1.0 g.) in tetrahydrofuran (20 ml.) under nitrogen at room temperature is added a solution of lithium tri-t-butoxyaluminium hydride (1.24 g.) in tetrahydrofuran (20 ml.). The mixture is stirred for 20 minutes at room temperature and poured into ice-water. Dilution with ether, washing the organic layer with saturated aqueous sodium bicarbonate, brine, drying over anhydrous sodium sulphate and stripping *in vacuo* gives a gum. Crystallisation from ether/hexane affords 0.78 g. of product; m.p. 157—162°C; λ^{KBr}_{max} 2.90, 5.80, 5.88, 6.12 and 6.22 μ; λ^{EtOH}_{max} 248 mμ (ϵ 18,700).

(f) *dl* - 13,β - Ethyl - 17α - hydroxy - 6 - methylene - 18,19 - dinorpregn - 4 - ene - 3,20 - dione acetate:—To a solution of *dl* - 13,β - ethyl - 17 - hydroxy - 6 - hydroxymethyl - 3 - methoxy - 18,19 - dinorpregna - 3,5 - dien - 20 - one acetate (0.73 g.) and oxalic acid dihydrate (0.73 g.) in methanol (73 ml.) is added water (30 ml.) at room temperature. After 5 minutes a precipitate begins to form. After 45 minutes at room temperature the mixture is poured into saturated aqueous sodium bicarbonate, extracted with ether, the extract washed with brine, dried over anhydrous sodium

sulphate and stripped *in vacuo*. The residue is triturated with ether/hexane giving 0.53 g. of product; m.p. 226—252°C (turns brown); λ_{max}^{KBr} 5.80, 5.88, 6.00, 6.19, 6.29, 10.93 μ; λ_{max}^{EtOH} 266 mμ (ϵ 10,900).

(g) *dl* - 13β - Ethyl - 17α - hydroxy - 6α - methyl - 18,19 - dinorpregn - 4 - ene - 3,20 - dione acetate:—Using the same conditions as for Example 1, step (e), the compound of this Example, step (f) is converted to the title compound which had m.p. 160—163°C; λ_{max}^{KBr} 5.80, 5.84 (shoulder), 6.01, 6.22 μ; λ_{max}^{EtOH} 240 mμ.

Analysis: Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.7.
Found: C, 74.27; H, 8.65.

EXAMPLE 5

d-13β-Ethyl-17α-hydroxy-6-methyl-18,19-dinorpregna-4,6-diene-3,20-dione

Following the procedure for Example 3, *d*-13β-ethyl-17α-hydroxy-6-methylene-18,19-dinorpregn-4-ene-3,20-dione is converted to the title compound.

EXAMPLE 6

13β-Ethyl-6α-chloro-18,19-dinorpregn-4-en-3-on-20ξ-ol acetate and 13β-Ethyl-6α-bromo-18,19-dinorpregn-4-en-3-on-20-ol acetate

(a) *dl* - 13β - Ethyl - 18,19 - dinorpregna - 3,5(6) - diene - 3,20 - diol - 3,20 - diacetate:—*dl* - 13β - Ethyl - 3 - methoxy - 18,19 - dinorpregna - 2,5(10) - dien - 20ξ - ol is hydrolysed in a mixture of methanol: concentrated HCl: water, 90:6:4 respectively (50 ml.) for one hour with stirring. The product is filtered off directly and washed with water. After drying, the crude *dl* - 13β - ethyl - 18,19 - dinorpregn - 4 - en - 3 - on - 20ξ - ol (0.75 g.) has m.p. 170—175°C, λ_{max}^{EtOH} 242 (ϵ 14,400). IR shows 6.01 μ and 6.19 μ.

This material is suspended in a mixture of acetic anhydride (4.8 ml.), ethyl acetate (45 ml.) and 70% perchloric acid (0.01 ml.) and stirred for 15—20 minutes. The excess acetic anhydride is destroyed by shaking with saturated sodium bicarbonate solution and the organic layer evaporated giving the title product.

(b) *dl* - 13β - Ethyl - 6α - chloro - 18,19 - dinorpregn - 4 - en - 3 - on - 20ξ - ol acetate:—*dl* - 13 - Ethyl - 18,19 - dinorpregna - 3,5(6) - diene - 3,20 - diol 3,20 - diacetate (1 g) is added to a mixture of acetone (23 ml.), water (6 ml.), sodium acetate (0.7 g.) and acetic acid (0.7 ml.). The mixture is cooled to 5°C, then treated with 8.3 g. of N-chlorosuccinimide. After 1¼ hours water is added and the product extracted with ether. The organic layer is evaporated and the product is obtained as a residue.

(c) 13β-Ethyl-6α-bromo-18,19-dinorpregn-4-en-3-on-20ξ-ol acetate:—The procedure of step (b) is repeated substituting N-bromosuccinimide for the chloro compound and the named product is obtained.

EXAMPLE 7

13β-Ethyl-6-chloro-18,19-dinorpregna-4,6-dien-3-on-20ξ-ol acetate and 20-alcohol

(a) *dl*-13β-Ethyl-18,19-dinorpregna-4,6-dien-3-on-20ξ-ol acetate:—The product of Example 6, step (c) is refluxed in dimethylformamide (50 ml.) with 3 g. of calcium carbonate for 1 hour under nitrogen. The solid is filtered off and the filtrate poured into water and extracted with ether. Evaporation of the solvent gives the title compound.

(b) *dl*-13β-Ethyl-18,19-dinor-6α,7α-oxidopregn-4-en-3-on-20ξ-ol acetate:—13β-Ethyl-18,19-dinorpregna-4,6-dien-3-on-20ξ-ol acetate (1 g.) in chloroform (50 ml.) is treated with monoperphthalic acid (24 ml. of 0.67 M) for 48 hours at room temperature. The organic phase is washed with saturated sodium bicarbonate then brine, and dried over sodium sulphate. Evaporation of the solvent gives the title compound.

(c) *dl*-13β-Ethyl-6-chloro-18,19-dinorpregna-4,6-dien-3-on-20-ol acetate, and 20-alcohol:—*dl*-13β-Ethyl-18,19-dinor-6α,7α-oxidopregn-4-en-3-on-20ξ-ol acetate (1 g.), is suspended in glacial acetic acid (50 ml.). A slow stream of dry hydrogen chloride is passed through the mixture at a temperature close to the freezing point of acetic acid (16.6°C). After 2—6 hours, the mixture is poured into ice water and extracted with benzene ether (10:1). The organic layer is washed free from acid, then dried and evaporated to give the title compound. Treatment of this material with 2% methanolic potassium hydroxide yields the corresponding alcohol at C—20.

An alternative procedure for preparation of the title compound is to take the *dl*-13β-ethyl-6α-chloro-18,19-dinorpregn-4-en-3-on-20ξ-ol acetate of Example 6, step (b) (1 g.) in ethyl acetate (25 ml.), acetic acid (5 ml.) and reflux with chloranil (2 g.)

for 24 hours under nitrogen. The mixture is cooled, washed with sodium hydroxide solution (10%) then brine, and dried. Evaporation gives *dl*-13β-ethyl-6-chloro-18,19-dinorpregna-4,6-dien-3-on-20-ol acetate.

The procedure of this Example, step (c) is repeated substituting dry hydrogen bromide and hydrogen fluoride, respectively, for hydrogen chloride. There are obtained *dl*-13β-ethyl-6-bromo-18,19-dinorpregna-4,6-dien-3-on-20ξ-ol acetate and 20-alcohol; and *dl*-13β-ethyl-6-fluoro-18,19-dinorpregna-4,6-dien-3-on-20ξ-ol acetate and 20-alcohol.

Example 8

13β-Ethyl-6α-chloro-18,19-dinorpregn-4-ene-3,20-dione-17α-ol acetate

(a) *dl*-13β-Ethyl-18,19-dinorpregna-3,5(6)-dien-20-(one-3,17α-diol diacetate:—Using the same conditions as for Example 6, step (a), *dl*-13β-ethyl-3-methoxy-18,19-dinorpregna-2,5(10)-dien-20-on-17α-ol is converted to the title compound.

(b) *dl*-13β-Ethyl-6α-chloro-18,19-dinorpregn-4-en-3,20-dion-17α-ol acetate:—Using the same conditions as for Example 6, step (b), *dl*-13β-ethyl-18,19-dinorpregna-3,5(6)-dien-20-one-3,17α-diol diacetate, is converted to the product.

Example 9

13β-Ethyl-6-chloro-18,19-dinorpregna-4,6-dien-3,20-dion-17α-ol acetate, and 17α-alcohol

(a) *dl*-13β-Ethyl-18,19-dinorpregna-4,6-diene-3,20-dion-17α-ol acetate—The product of Example 8, step (b) is heated with dimethylformamide and calcium carbonate according to the procedure of Example 7, step (a) and the named compound is obtained.

(b) *dl*-13β-Ethyl-18,19-dinor-6α,7α-oxidopregn-4-ene-3,20-dion-17α-ol, acetate:—Using the same conditions as for Example 7, step (b), *dl*-13β-ethyl-18,19-dinorpregna-4,6-dien-3,20-dione-17α-ol, acetate, is converted to the title compound.

(c) *dl*-13β-Ethyl-6-chloro-18,19-dinorpregna-4,6-diene-3,20-dion-17α-ol acetate and 17α-alcohol:—Using the same conditions as for Example 7, step (c) *dl*-13β-ethyl-18,19-dinor-6α,7α-oxidopregn-4-ene-3,20-dione-17α-ol acetate is converted to the title compound. The *dl*-form had m.p. 198—200°C; λ_{max}^{KBr} 5.78, 5.85, 5.99, 6.23, 6.31 (shoulder); λ_{max}^{EtOH} 283 mμ (ε 23,000).

Analysis: Calcd. for $C_{23}H_{29}ClO_4$: C, 68.23; H, 7.22, Cl, 8.76.
Found: C, 68.60; H, 6.56; Cl, 8.79.

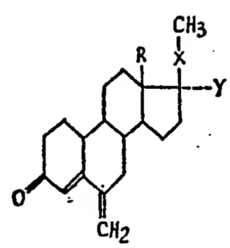
Alternatively, using the conditions of the second method in Example 7, step (c), *d*-13β-ethyl-6ξ-chloro-18,19-dinorpregn-4-ene-3,20-dione-17α-ol acetate is converted to the title compound.

The 17-acetate group in the compound of this Example is hydrolysed with 2% methanolic potassium hydroxide according to Example 7 and the 17α-alcohol is obtained.

Similarly, following the procedure of Example 7, the corresponding *d*-13β-ethyl-6-bromo-18,19-dinorpregna-4,6-diene-3,20-dion-17α-ol acetate and 17-alcohol and *d*-13β-ethyl-6-fluoro-18,19-dinorpregna-4,6-diene-3,20-dion-17α-ol acetate and 17-alcohol are prepared.

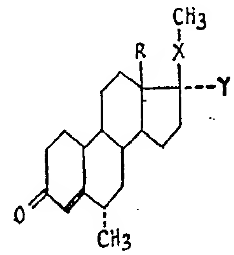
Example 10

The procedure of Example 1, step (e) is repeated, substituting for the 13β-ethyl-20ξ-hydroxy-6-methylene-18,19-dinorpregn-4-en-3-one, stoichiometrical amounts of the following *d*-compounds:



R		
$CH_2CH_2CH_3$	C(H)OH	H
$CH_2(CH_2)_4CH_3$	C(H)OH	H
$CH(CH_3)_2$	C(H)OH	H
CH_2CH_3	C(H)OH	$OCOCH_3$
CH_2CH_3	C=O	OH
CH_2CH_3	C=O	$OCOCH_3$
CH_2CH_3	C=O	$OCOCH_2(CH_2)_4CH_3$
CH_2CH_3	$C(H)OCOCH_3$	H

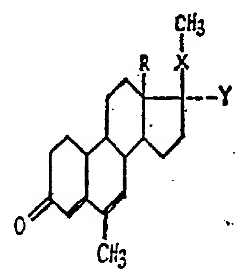
There are obtained the following *d*-compounds:



R	X	Y
$CH_2CH_2CH_3$	C(H)OH	H
$CH_2(CH_2)_4CH_3$	C(H)OH	H
$CH(CH_3)_2$	C(H)OH	H
CH_2CH_3	C(H)OH	$OCOCH_3$
CH_2CH_3	C=O	OH
CH_2CH_3	C=O	$OCOCH_3$
CH_2CH_3	C=O	$OCOCH_2(CH_2)_4CH_3$
CH_2CH_3	$C(H)OCOCH_3$	H

EXAMPLE 11

The procedure of Example 3 is repeated substituting for the 13β-ethyl-20ξ-hydroxy-6-methylene-18,19-dinorpregn-4-en-3-one, stoichiometrical amounts of the corresponding 6-methylene *d*-compounds of Example 10. There are obtained the following *d*-compounds:

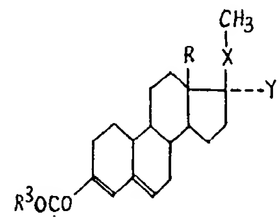


R	X	Y
$CH_2CH_2CH_3$	C(H)OH	H
$CH_2(CH_2)_4CH_3$	C(H)OH	H
$CH(CH_3)_2$	C(H)OH	H
CH_2CH_3	C(H)OH	$OCOCH_3$
CH_2CH_3	C=O	$OCOCH_3$
CH_2CH_3	C=O	$OCOCH_2(CH_2)_4CH_3$
CH_2CH_3	$C(H)OCOCH_3$	H

By the same procedure, 13β-ethyl-6-methylene-18,19-dinorpregn-4-ene-3,20-dione is rearranged to 13β-ethyl-6-methyl-18,19-dinorpregna-4,6-diene-3,20-dione.

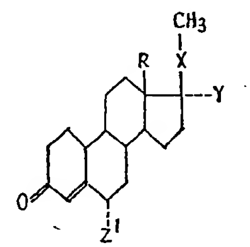
EXAMPLE 12

The procedure of Example 6 steps (b) and (c) are repeated, substituting for the 13β-ethyl-18,19-dinorpregna-3,5(6)-diene-3,20-diol 3,20-diacetate, stoichiometrical amounts of the following *d*-compounds:



R	X	Y	R^3
$CH_2CH_2CH_3$	C(H)$OCOCH_3$	H	CH_3
$CH_2(CH_2)_4CH_3$	C(H)$OCOCH_3$	H	CH_3
CH_2CH_3	C(H)$OCOCH_2(CH_2)_4CH_3$	H	$CH_2(CH_2)_4CH_3$
CH_2CH_3	C=O	H	CH_3
CH_2CH_3	C(H)OH	OH	CH_3
CH_2CH_3	C(H)$OCOCH_3$	$OCOCH_3$	CH_3

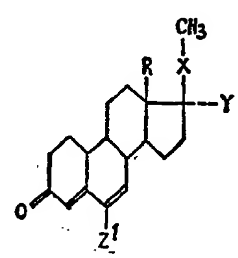
The following *d*-compounds are obtained:



R	X	Y	Z^1
$CH_2CH_2CH_3$	CH(H)$OCOCH_3$	H	Cl
$CH_2CH_2CH_3$	C(H)$OCOCH_3$	H	Br
$CH_2(CH_2)_4CH_3$	C(H)$OCOCH_3$	H	Cl
$CH_2(CH_2)_4CH_3$	C(H)$OCOCH_3$	H	Br
CH_2CH_3	C(H)$OCOCH_2(CH_2)_4CH_3$	H	Cl
CH_2CH_3	C(H)$OCOCH_2(CH_2)_4CH_3$	H	Br
CH_2CH_3	C=O	H	Cl
CH_2CH_3	C=O	H	Br
CH_2CH_3	C(H)OH	OH	Cl
CH_2CH_3	C(H)OH	OH	Br
CH_2CH_3	C(H)$OCOCH_3$	$OCOCH_3$	Cl
CH_2CH_3	C(H)$OCOCH_3$	$OCOCH_3$	Br

EXAMPLE 13

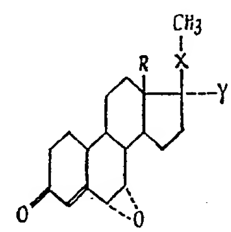
The procedure of Example 7, step (c), the chloranil dehydration, is repeated, substituting for the 13β-ethyl-6α-chloro-18,19-dinorpregn-4-en-3-on-20ξ-ol acetate, stoichiometrical amounts of the products of Example 12. There are obtained the following *d*-compounds:



R	X	Y	Z^1
$CH_2CH_2CH_3$	$C(H)OCOCH_3$	H	Cl
$CH_2CH_2CH_3$	$C(H)OCOCH_3$	H	Br
$CH_2(CH_2)_4CH_3$	$C(H)OCOCH_3$	H	Cl
$CH_2(CH_2)_4CH_3$	$C(H)OCOCH_3$	H	Br
CH_2CH_3	$C(H)OCOCH_2(CH_2)_4CH_3$	H	Cl
CH_2CH_3	$C(H)OCOCH_2(CH_2)_4CH_3$	H	Br
CH_2CH_3	C=O	H	Cl
CH_2CH_3	C=O	H	Br
CH_2CH_3	C(H)OH	OH	Cl
CH_2CH_3	C(H)OH	OH	Br
CH_2CH_3	$C(H)OCOCH_3$	$OCOCH_3$	Cl
CH_2CH_3	$C(H)OCOCH_3$	$OCOCH_3$	Br

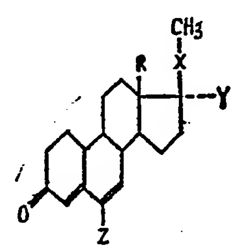
Example 14

The procedure of Example 7, step (c), the opening of the 6α,7α-epoxide ring with hydrogen chloride, hydrogen bromide and hydrogen fluoride, is repeated, substituting for 13β-ethyl-18,19-dinor-6α,7α-oxidopregn-4-en-3-on-20ξ-ol acetate, stoichiometrical amounts of the following *d*-compounds:



R	X	Y
$CH_2CH_2CH_3$	$C(H)OCOCH_3$	H
$CH_2(CH_2)_4CH_3$	$C(H)OCOCH_3$	H
CH_2CH_3	$C(H)OCOCH_2(CH_2)_4CH_3$	H
CH_2CH_3	C=O	H
CH_2CH_3	C(H)OH	OH
CH_2CH_3	$C(H)OCOCH_3$	$OCOCH_3$

There are obtained the following *d*-compounds:



R	X	Y	Z
$CH_2CH_2CH_3$	$C(H)OCOCH_3$	H	Cl
$CH_2CH_2CH_3$	$C(H)OCOCH_3$	H	Br
$CH_2CH_2CH_3$	$C(H)OCOCH_3$	H	F
$CH_2(CH_2)_4CH_3$	$C(H)OCOCH_3$	H	Cl
$CH_2(CH_2)_4CH_3$	$C(H)OCOCH_3$	H	Br
$CH_2(CH_2)_4CH_3$	$C(H)OCOCH_3$	H	F
CH_2CH_3	$C(H)OCOCH_2(CH_2)_4CH_3$	H	Cl
CH_2CH_3	$C(H)OCOCH_2(CH_2)_4CH_3$	H	Br
CH_2CH_3	$C(H)OCOCH_2(CH_2)_4CH_3$	H	F
CH_2CH_3	C=O	H	Cl
CH_2CH_3	C=O	H	Br
CH_2CH_3	C=O	H	F
CH_2CH_3	C(H)OH	OH	Cl
CH_2CH_3	C(H)OH	OH	Br
CH_2CH_3	C(H)OH	OH	F
CH_2CH_3	$C(H)OCOCH_3$	$OCOCH_3$	Cl
CH_2CH_3	$C(H)OCOCH_3$	$OCOCH_3$	Br
CH_2CH_3	$C(H)OCOCH_3$	$OCOCH_3$	F

EXAMPLE 15

13β-Ethyl-17α-hydroxy-6-methyl-18,19-dinorpregna-4,6-diene-3,20-dione acetate

(a) *dl* - 13β - Ethyl - 17α - hydroxy - 6 - hydroxymethyl - 3 - methoxy - 18,19 - dinorpregna - 3,5 - dien - 20 - one acetate:—To a solution of *dl* - 13β - ethyl - 6 - formyl - 17α - hydroxy - 3 - methoxy - 18,19 - dinorpregna - 3,5 - dien - 20 - one acetate (1.0 g.) in tetrahydrofuran (freshly distilled, 20.0 ml.) under nitrogen at room temperature is added a solution of lithium tri-*t*-butoxyaluminium hydride (1.24 g.) in tetrahydrofuran (freshly distilled, 20.0 ml.) all at once. After 20 minutes at room temperature the mixture is poured into ice-water. Extraction with ether, washing the organic layer with saturated aqueous sodium bicarbonate, brine, drying over anhydrous sodium sulphate and stripping *in vacuo* provides a gum. Crystallisation from ether/hexane affords 0.78 g. of slightly yellow coloured solid; m.p. 157—162°C; λ^{KBr}_{max} 2.90, 5.80 and 5.88 μ; λ^{EtOH}_{max} 248 mμ (ε 18,700).

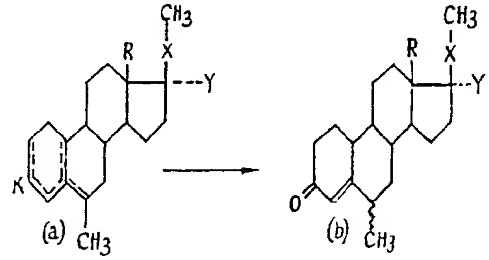
(b) *dl* - 13β - Ethyl - 17α - hydroxy - 6 - methylene - 18,19 - dinorpregn - 4 - ene - 3,20 - dione acetate:—To a solution of oxalic acid dihydrate (3.2 g.) in methanol (320 ml.) is added *dl* - 13β - ethyl - 6 - hydroxymethyl - 3 - methoxy - 18,19 - dinorpregna - 3,5 - dien - 20 - one acetate (3.00 g.). Water (132 ml.) is added and the mixture is stirred at room temperature for 45 minutes. The mixture is poured into saturated aqueous sodium bicarbonate, extracted with ether and the extracts washed with brine and dried over anhydrous sodium sulphate. Evaporation *in vacuo* yields a solid which is triturated with ether to give 2.25 g. of light yellow coloured product; m.p. 225—246°C. (decomposes); λ^{KBr}_{max} 5.80—5.83, 6.02 μ; λ^{EtOH}_{max} (on a previously prepared sample) 226 mμ (ε 10,900).

(c) *dl* - 13β - Ethyl - 17α - hydroxy - 6 - methyl - 18,19 - dinorpregna - 4,6 - diene - 3,20 - dione acetate:—A mixture of *dl* - 13β - ethyl - 17α - hydroxy - 6 - methylene - 18,19 - dinorpregn - 4 - ene - 3,20 - dione acetate (0.50 g.), Pd/C (5%, 75 mg.) and sodium acetate (0.25 g.) in absolute ethanol (15 ml.) is heated at reflux for 45 minutes after which time a sample shows UV absorption at 287 mμ and no 266 mμ absorption. After cooling to room temperature the mixture is filtered through fitler aid and diluted with ether. Washing with saturated aqueous sodium sulphate and stripping *in vacuo* yields a gum. Column chromatography on Grade III Woelm neutral alumina using 100% benzene as eluant affords 0.28 g of colourless product on crystallisation from ether/hexane; m.p. 190—191°C; λ^{KBr}_{max} 5.80—5.90, 6.09, 6.21 (weak), 6.30 μ (weak); λ^{EtOH}_{max} 287 mμ (ε 24,200); NMR has methyl singlets at 1.93, 2.10 and 2.14 ppm and vinyl protons at 5.93 and 6.02 ppm.

Analysis: Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H ,8.39.
Found: C, 74.84; H, 8.38.

The 6-methyl compounds of this invention may a

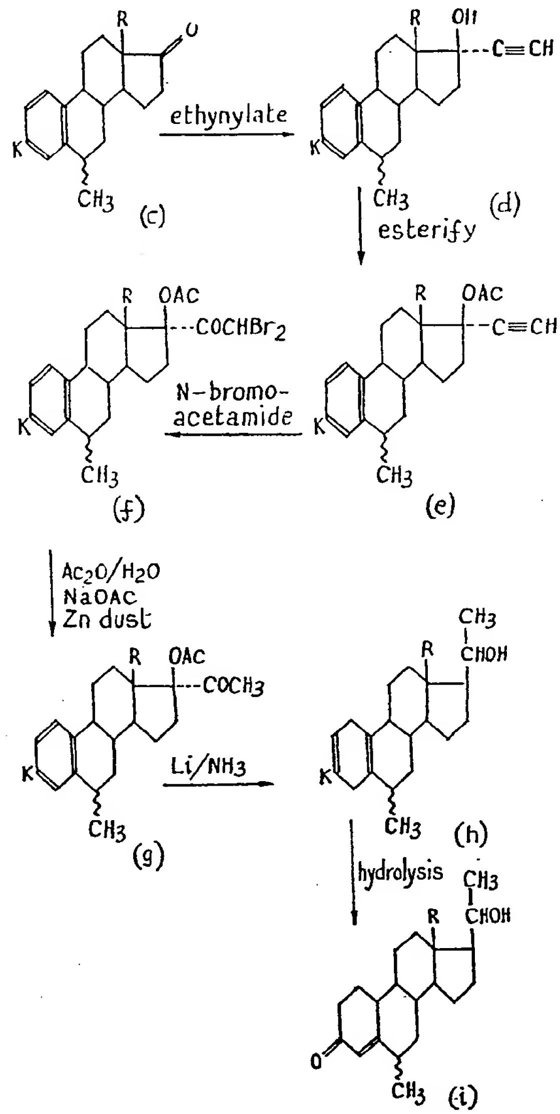
a compound of the formula:



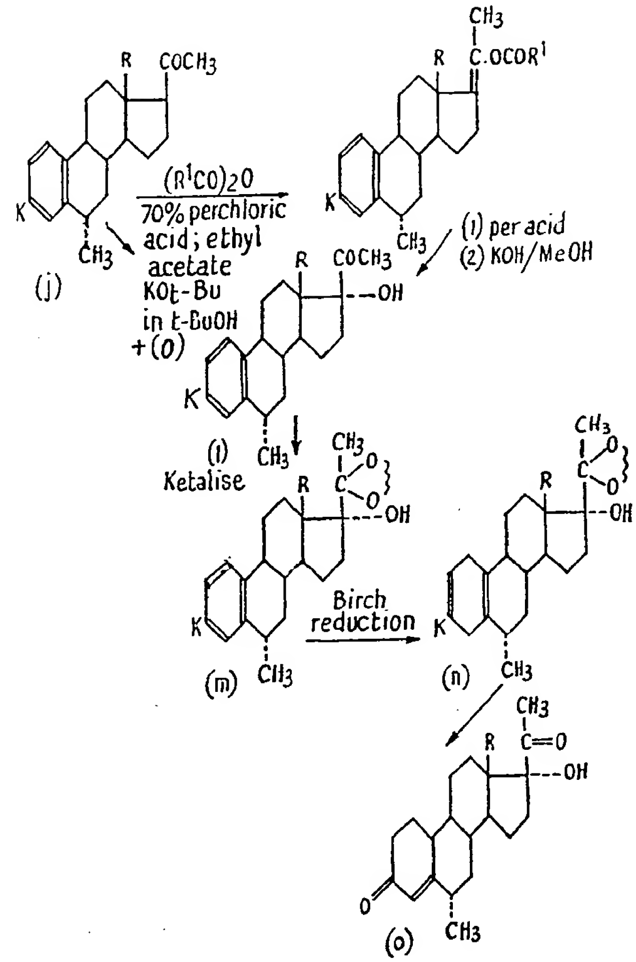
where K is a protected oxo group which in conjunction with unsaturation in rings A and/or B indicated by dotted lines is hydrolysable by acid to a 4,5-ethylenic 3-ketone. Protected oxo groups are well known in steroid chemistry and suitable starting materials can be prepared from known 6-methyl compounds, e.g. the 6-methyl gonatrienes described in British Patent Specification 1,103,205. Preferred starting materials for the above process are 2,5(10)-dienes in which K is an alkoxy group of 3-acyloxy-3,5-dienes in which K is an acyloxy group. X may be protected, e.g. when carbonyl, by a ketal group. The product of the above reaction predominantly has the 6α-methyl group but may be accompanied by the 6β-methyl compound.

Thus 3-alkoxy-2,5(10)-diene starting materials for the above process where X is hydroxymethylene and Y is hydrogen may be prepared from 13β-alkyl-3-alkoxy 6-methylgona-1,3,5(10)-trien-17-ones described in British Specification 1,103,205 by the following procedure. The 17-one starting material is ethynylated by a standard method followed by conversion of the resulting 17α-ethynyl-17β-ol by acylation and treatment with N-bromoacetamide to give a 17α-dibromoacetyl group and debromination with zinc and acetic acid to give a 17α-acetyl-17β-acetoxy compound which is subjected to Birch reduction to give a 17β-(α-hydroxyethyl)-3-alkoxy-13β-alkyl-6-methylgona-2,5(10-diene compound which is then hydrolysed according to the above process of the

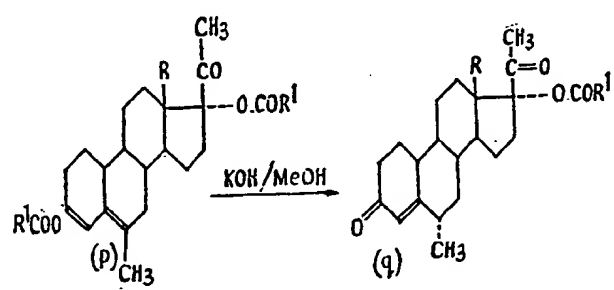
invention. The preparation of the starting material is illustrated by the following scheme:



Other starting materials (a) for the hydrolysis process may be prepared, for example, by selective oxidation of the intermediate (h) prior to hydrolysis, giving a compound where X is carbonyl. A starting material (a) where K is an alkoxy group



A 17-acetyl 3-alkoxy-13β-alkyl-6-methylgona-1,3,5(10)-triene (j), obtained for example by oxidation including A-aromatisation of compound (h) above, is converted to the corresponding 17β-acetyl-17α-hydroxy compound *l* either by treatment with potassium *t*-butoxide in *t*-butanol in the presence of oxygen or by treatment with an acid anhydride $(R^1CO)_2O$ where R^1 is a lower alkyl group in 70% perchloric acid and ethyl acetate to give compound (K) which on treatment with a peracid followed by potassium hydroxide in methanol yields the compound (1). Compound (1) is ketalised by standard methods, e.g. ethylene glycol in benzene with *p*-toluene sulphonic acid as catalyst, to give the ketal (m) which is reduced by a Birch reduction reaction (e.g. Li in liquid ammonia in the presence of *t*-butanol) to give compound (n) which is a starting material for the process (a) to (b). Upon hydrolysis with acid, e.g. HCl in methanol, compound (b) is obtained wherein X is carbonyl and Y is hydroxy (i.e. compound o). The corresponding compound where Y is acyl may be obtained by acylation of compound (o) to give the corresponding 3,17-diacyl-3,5-diene, partial hydrolysis of which gives

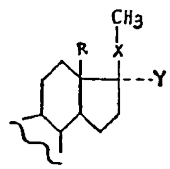


compound (q).

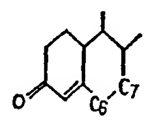
A compound of the invention which has a 4,5-ethylenic bond in ring A and no unsaturation in ring B can be produced by isomerisation, using standard methods, of the corresponding compound with a 5(10)-ethylenic bond. The latter can be obtained for example by treatment of a 3-alkoxy-2,5(10)-diene under mild hydrolysis conditions as with oxalic acid.

WHAT WE CLAIM IS:—

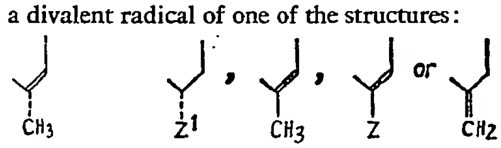
1. A steroid compound having in rings C and D the structure:



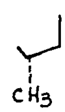
wherein R is an alkyl group of from 2 to 6 carbon atoms; X is C=O or C(H)OR[1] wherein R[1] is hydrogen or a (lower)alkanoyl group; and Y is H, OH or OCOR[2] wherein R[2] is a (lower)alkyl group; and having in rings A and B the structure:



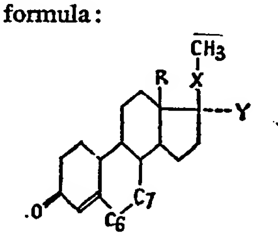
wherein —C_6—C_7— is a divalent radical of one of the structures:



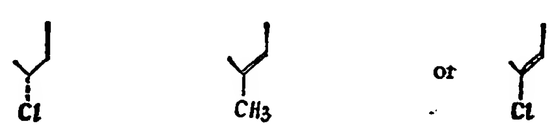
wherein Z is chloro, bromo or fluoro and Z[1] is chloro or bromo provided that when X is C=O and Y is H, —C_6—C_7— is other than



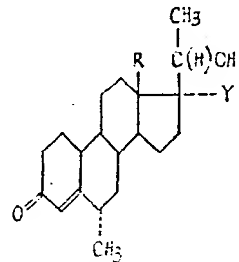
2. A compound as defined in Claim 1, but wherein a 6-methyl group is present in a saturated ring B and this has the β-configuration.
3. A compound as claimed in Claim 1, wherein R is an ethyl group.
4. A compound as claimed in Claim 1 or Claim 3, wherein R[1] is an acetyl group.
5. A compound as claimed in any one of Claims 1, 3 or 4, wherein R[2] is a methyl group.
6. A compound of the formula:



wherein R is an alkyl group of from 2 to 6 carbon atoms; X is C=O or C(H)OR[1] wherein R[1] is hydrogen or a (lower)alkanoyl group; Y is H, OH or OCOR[2] wherein R[2] is a (lower)alkyl group; and —C_6—C_7— is a divalent radical of one of the structures:

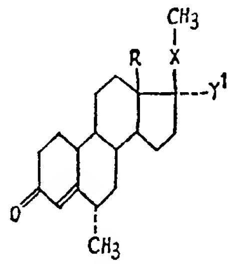


7. A compound of the formula:



wherein R is an alkyl group of from 2 to 6 carbon atoms; and Y is H, OH or $OCOR^2$ wherein R^2 is a (lower)alkyl group.

8. A compound of the formula:



wherein R is an alkyl group of from 2 to 6 carbon atoms; X is C=O or C(H)OH; and Y^1 is OH or $OCOR^2$ wherein R^2 is a (lower)alkyl group.

9. A compound as claimed in any one of Claims 6, 7 or 8 wherein R is an ethyl group.

10. 13β-Ethyl-20ξ-hydroxy-6-methyl-18,19-dinorpregna-4,6-dien-3-one.

11. 13β-Ethyl-6-methyl-18,19-dinorpregna-4,6-diene-3,20-dione.

12. 13β-Ethyl-17α-hydroxy-6-methyl-18,19-dinorpregna-4,6-diene-3,20-dione.

13. The 17-acetate ester of the compound of Claim 12.

14. 13β-Ethyl-6α-chloro-18,19-dinorpregn-4-en-3-on-20-ol acetate.

15. 13β-Ethyl-6-chloro-18,19-dinorpregna-4,6-dien-3-on-20-ol acetate.

16. 13β-Ethyl-6α-chloro-18,19-dinorpregn-4-ene-3,20-dion-17α-ol acetate.

17. 13β-Ethyl-6-chloro-18,19-dinorpregna-4,6-diene-3,20-dion-17α-ol acetate.

18. 13β-Ethyl-6-chloro-17α-hydroxy-18,19-dinorpregna-4,6-diene-3,20-dione.

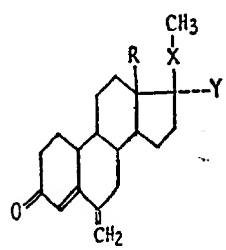
19. 13β-Ethyl-20ξ-hydroxy-6α-methyl-18,19-dinorpregn-4-en-3-one.

20. 13β-Ethyl-17α-hydroxy-6α-methyl-18,19-dinorpregn-4-ene-3,20-dione acetate.

21. 13β-Ethyl-20ξ-hydroxy-6-methylene-18,19-dinorpregn-4-en-3-one.

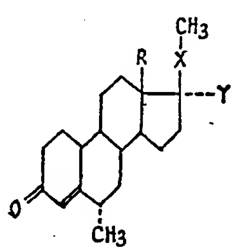
22. A process for the preparation of a compound as claimed in Claim 1 which comprises

(a) hydrogenating a compound of the formula II:

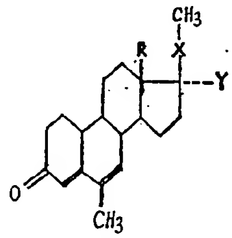


(II)

to give a compound of the formula Id:

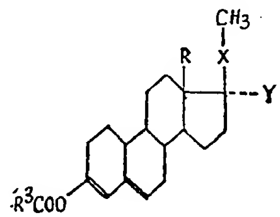


(b) rearranging a compound of the formula II as above defined to a compound of the formula Ie:



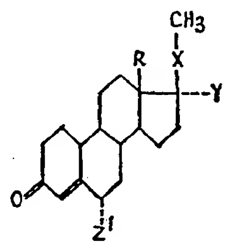
(Ie)

(c) halogenating a compound of the formula III:



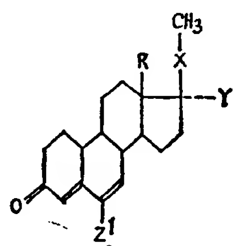
(III)

to give a compound of the formula If, wherein Z^1 is chlorine or bromine,



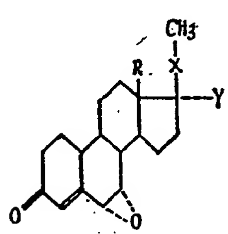
(If)

(d) dehydrogenating a compound of the formula If as above defined to give a compound of the formula Ig



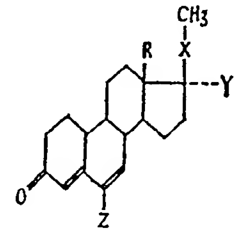
(Ig)

(e) reacting a compound of the formula IV



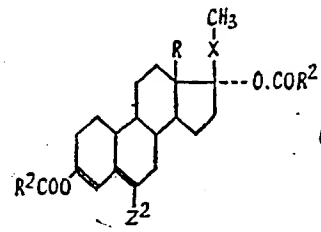
(IV)

with a hydrogen halide to form a compound of the formula Ih:



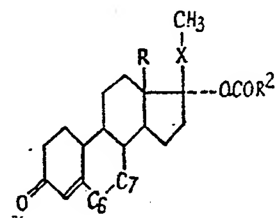
(Ih)

(f) partially hydrolysing a compound of the formula Ik



(Ik)

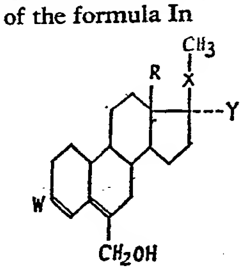
wherein X is as defined in Claim 1 and Z^2 is methyl, bromo or chloro to give a compound of formula Ij:



(Ij)

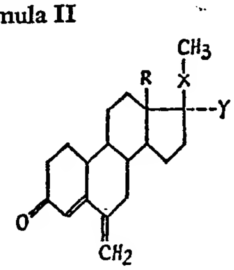
wherein C_6—C_7 is a divalent radical as defined in claim 1 and having a saturated ring B, with a 6-methyl, chloro or bromo substituent,

(g) hydrolysing a compound of the formula In



(In)

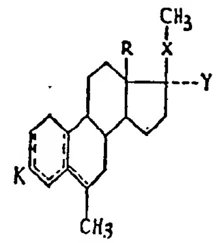
to give a compound of the formula II



(II)

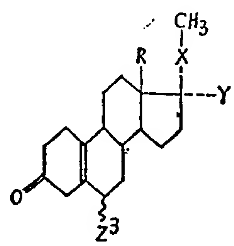
the groups R, X, Y, Z, Z^1 —C_6—C_7—, R^1 and R^2 in the above formulae being as defined in Claim 1 (unless otherwise specified), W being an alkoxy group and R^3 being a lower alkyl radical.

23. A process for preparing a compound as claimed in Claim 1 or Claim 2 wherein Ring B is saturated which process comprises hydrolysing a compound of the formula



(a)

where K is a protected oxo group which in conjunction with unsaturation in Rings A and/or B indicated by dotted lines is hydrolysable by acid to a 4,5-ethylenic 3-ketone, and X is as defined in Claim 1 or may be a protected carbonyl or hydroxymethylene group and Y is defined in Claim 1 to obtain a compound of formula Id and/or the corresponding 6β-methyl compound or isomerising a compound of formula:



(Io)

wherein Z^3 is methyl, α-chloro or α-bromo to obtain a corresponding gon-4-en-3-one, the groups R, X, Y, Z, Z^1, —C_6—C_7, R^1, R^2 and W in the above formulae being as defined in Claim 1 (unless otherwise specified above) and R^3 being a lower alkyl radical.

24. A process as claimed in Claim 22, wherein R is an ethyl group.

25. A process as claimed in Claim 22 or 24 wherein a compound of the formula II is hydrogenated by exchange hydrogenation with an organic hydrogen donor in the presence of a catalyst to obtain a compound of the formula Id.

26. A process as claimed in Claim 25, wherein the exchange hydrogenation is performed with cyclohexene in the presence of a palladium on carbon catalyst.

27. A process as claimed in Claim 22 or 24 wherein a compound of the formula II is rearranged to give a compound of the formula Ie by heating with a weak base in the presence of a noble metal catalyst.

28. A process as claimed in Claim 27 wherein the weak base is sodium acetate.

29. A process as claimed in Claim 27 or Claim 28 wherein the noble metal catalyst is a platinum or palladium catalyst.

30. A process as claimed in Claim 22 or 24 wherein a compound of the formula III is halogenated with N-chloro- or N-bromo-succinimide to give a compound of formula If.

31. A process as claimed in Claim 22 or 24 wherein a compound of the formula If is dehydrogenated by heating with chloranil to give a compound of formula Ig.

32. A process as claimed in Claim 22 or 24 wherein a compound of the formula IV is reacted with a hydrogen halide to obtain a compound of formula Ih.

33. A process as claimed in Claim 22 or 24 wherein a compound of the formula Ik is partially hydrolysed by dilute alkali metal hydroxide to give a compound of the formula Ij.

34. A process as claimed in Claim 33 wherein the hydrolysis is carried out with potassium hydroxide in methanol.

35. A process as claimed in Claim 22 or 24 wherein a compound of the formula In is hydrolysed with dilute mineral acid or an organic acid to a compound of the formula II.

36. A process as claimed in Claim 35 wherein the acid is dilute sulphuric acid or oxalic acid.

37. A process as claimed in Claim 35 or 36 wherein a compound of the formula In is used wherein W is a methoxy group.

38. A process as claimed in Claim 23, wherein K is an alkoxy group accompanied by ethylenic bonds in the 2- and 5(10)- r 3- and 5-positions.

39. A process for the preparation of a compound as claimed in Claim 1, wherein X is C=O, which process comprises selectively oxidising a corresponding compound where X is CHOH.

40. A process for the preparation of a compound as claimed in Claim 1, wherein X is CHOH, which process comprises selectively hydrolysing a corresponding compound wherein X is $CHOR^1$, R^1 being a lower alkanoyl group.

41. A process as claimed in Claim 22 or 24 substantially as described in any one of Examples 1 to 14.

42. A process as claimed in Claim 22 substantially as described in Example 15.

43. A steroid compound whenever prepared by a process as claimed in Claim 22 or 24.

44. A steroid compound whenever prepared by a process as claimed in any one of Claims 25 to 32.

45. A steroid compound whenever prepared by a process as claimed in Claim 33 or 34.

46. A steroid compound whenever prepared by a process as claimed in 35 or 36.

47. A steroid compound whenever prepared by a process as claimed in Claim 37.

48. A steroid compound whenever prepared by a process as claimed in Claim 23 or 38.

49. A steroid compound whenever prepared by a process as claimed in Claim 41.

50. 13β - Ethyl - 17α - hydroxy - 6 - methylene - 18,19 - dinorpregn - 4 - ene - 3,20 - dione acetate.

51. A steroid compound whenever prepared by a process as claimed in Claim 42.

52. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 and 3 to 20, (excluding 6-methylene compounds), and a pharmaceutical carrier.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1972.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.